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(54) Title: THERAPY OF PSORIASIS

(57) Abstract: The present invention provides for uses of an anti-TNFα antibody or an antigen-binding fragment thereof for the manufacture of a medicament for use in the treatment of psoriasis or psoriatic skin lesions in an individual in need thereof.

THERAPY OF PSORIASIS

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/167,470, filed November 24, 1999, the entire teachings of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Psoriasis is a multifactorial inherited condition characterized by the eruption of circumscribed, discrete and confluent, reddish, silvery-scaled maculopapules. The lesions occur predominately on the elbows, knees, scalp and trunk. The disease occurs throughout the world. In the temperate zones, about 2% of the population are affected. Psoriasis is representative of those diseases accompanied by an inflammatory cornification of the skin, and a number of patients suffering from psoriasis is increasing.

Hyperproliferation of keratinocytes is a key feature of psoriasis along with epidermal inflammation and reduced differentiation of keratinocytes. Psoriasis is also associated with elevated levels of inflammatory cytokines, including TNFα, IL-6 and TGFβ (see, for example, Bonifati *et al.*, *Clin. Exp. Dermatol.*, 19:383-387 (1994)).

Psoriatic arthritis is a chronic autoimmune disease that shares some features with both rheumatoid arthritis and psoriasis (for review, see Breathnach, *In Rheumatology*, Klippel and Dieppe, eds., 2nd edition, Mosby, 22.1-22.4 (1998)). However, psoriasis and psoriatic arthritis are different clinical entities, and are associated with somewhat different MHC haplotypes (Gladman, *Rheum. Dis. Clin. NA*, 18:247-256 (1992); Breathnach, *In Rheumatology*, Klippel and Dieppe, eds., 2nd edition, Mosby, 22.1-22.4 (1998)). The overall prognosis for psoriatic arthritis is far worse than for psoriasis.

Psoriatic skin lesions are present in patients with psoriatic arthritis, although only a minority of psoriasis sufferers actually have psoriatic arthritis. Psoriasis is

occasionally accompanied by joint pain, but does not involve the extreme pain and often deforming degeneration of joints and bone that occurs in patients with psoriatic arthritis.

Therapeutic efforts in psoriasis are aimed at decreasing the proliferative rate of the epidermis either by direct action on cell division, or through agents that reduce the inflammatory response or vascular permability. Therapeutic efforts in psoriasis are also aimed at promoting immunomodulation and avoidance of infection by bacteria and fungi.

Although the current therapies for psoriasis share the common feature of inhibiting hyperproliferation of keratinocytes, they act through different cellular mechanisms and are accompanied by a variety of side effects that are at best unpleasant and often dangerous. For example, tar based therapies are uncomfortable and a nuisance to apply. Moreover, tar stains the skin and has an odor. Immunosuppressants such as methotrexate can predispose to malignancy, cyclosporine can cause renal damage and hypertension, glucocorticoids can cause local and serious systemic side effects such as adrenal suppression, vitamin D analogs can cause disordered calcium metabolism, and retinoids can have a broad range of side effects and are teratogens. Phototherapy and photochemotherapy entailing the administration of the photosensitizing drug methoxsalen can cause altered immunologic effects and an increased risk of carcinogenesis. Because of the distressing and disfiguring nature of psoriasis and the unsatisfactory aspects of current therapies, there is a considerable interest in developing alternative therapeutic approaches for treating this hyperproliferative skin disorder.

SUMMARY OF THE INVENTION

The present invention provides uses of an anti-tumor necrosis factor alpha (anti-TNFα) antibody or an antigen-binding fragment thereof for the manufacture of a medicament for use in the treatment of psoriasis or psoriatic lesions in an individual in need thereof. In a preferred embodiment, the antibody is a chimeric antibody such as the cA2 monoclonal antibody (also known as infliximab and REMICADE® antibody).

The present invention also provides methods of treating psoriasis or psoriatic lesions in an individual in need thereof comprising administering to the individual a therapeutically effective amount of an anti-TNFα antibody or an antigen-binding fragment thereof. In a preferred embodiment, the antibody is a chimeric antibody such as the cA2 monoclonal antibody.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to methods of treating psoriasis or psoriatic (skin) lesions in an individual in need thereof comprising administering to the individual a therapeutically effective amount of a TNFα antagonist. The TNFα antagonist can be administered alone, as adjuvant and/or concomitant therapy to other therapeutic regimens or in combination with other therapeutic agents. The TNFα antagonist can also be administered in combination with one or more different TNFα antagonist.

In a particular embodiment, the present invention relates to a method of treating psoriasis in an individual in need thereof comprising administering to the individual a therapeutically effective amount of an anti-TNFα antibody or an antigen binding fragment thereof. In another embodiment, the invention relates to methods of treating psoriatic lesions in an individual in need thereof comprising administering to the individual a therapeutically effective amount of an anti-TNFα antibody or an antigen binding fragment thereof. In a further embodiment, the invention relates to methods of treating psoriatic arthritis in an individual in need thereof comprising administering to the individual a therapeutically effective amount of an anti-TNFα antibody or an antigen binding fragment thereof. In a preferred embodiment, the antibody is a chimeric antibody such as the cA2 monoclonal antibody.

As used herein, individuals (patients) are defined as having psoriasis if they lack the more serious symptoms of psoriatic arthritis (e.g., distal interphalangeal joint DIP involvement, enthesopathy, spondylitis and dactylitis), but exhibit one of the following: 1) inflamed swollen skin lesions covered with silvery white scale (plaque psoriasis or psoriasis vulgaris); 2) small red dots appearing on the trunk,

arms or legs (guttate psoriasis); 3) smooth inflamed lesions without scaling in the flexural surfaces of the skin (inverse psoriasis); 4) widespread reddening and exfoliation of fine scales, with or without itching and swelling (erythrodermic psoriasis); 5) blister-like lesions (pustular psoriasis); 6) elevated inflamed scalp lesions covered by silvery white scales (scalp psoriasis); 7) pitted fingernails, with or without yellowish discoloration, crumbling nails, or inflammation and detachment of the nail from the nail bed (nail psoriasis).

Tumor Necrosis Factor Alpha Antagonists

As used herein, a "tumor necrosis factor alpha antagonist" decreases, blocks, inhibits, abrogates or interferes with TNFα activity *in vivo*. For example, a TNFα antagonist can bind TNFα and includes anti-TNFα antibodies, antigen binding fragments thereof, and TNFα receptor molecules and derivatives which bind specifically to TNFα. A TNFα antagonist can also prevent or inhibit TNFα synthesis and/or TNFα release and includes compounds such as thalidomide, tenidap, and phosphodiesterase inhibitors, such as, but not limited to, pentoxifylline and rolipram. A TNFα antagonist that can prevent or inhibit TNFα synthesis and/or TNFα release also includes A2b adenosine receptor enhancers and A2b adenosine receptor agonists (e.g., 5'-(N-cyclopropyl)-carboxamidoadenosine, 5'-N-ethylcarboxamidoadenosine, cyclohexyladenosine and R-N^6-phenyl-2-propyladenosine). See, for example, Jacobson, GB 2 289 218 A, the teachings of which are entirely incorporated herein by reference. A TNFα antagonist can also prevent or inhibit TNFα receptor signalling and includes mitogen activated protein (MAP) kinase inhibitors (e.g., SB 203580; Lee and Young, *J. Leukocyte Biol.*, *59*:152-157 (1996), the teachings of which are entirely incorporated herein by reference). A TNFα antagonist can inhibit or interfere with the binding of TNFα to its receptors and/or the cytotoxic effect of TNFα (see, e.g., Wallach *et al.*, U.S. Patent No. 5,695,953; and Wallach *et al.*, U.S. Patent No. 5,981,701, which references are entirely incorporated herein by reference). Other TNFα antagonists include agents which decrease, block, inhibit, abrogate or interfere with membrane TNFα cleavage, such as, but not limited to, metalloproteinase inhibitors; agents

which decrease, block, inhibit, abrogate or interfere with TNFα activity, such as, but not limited to, angiotensin converting enzyme (ACE) inhibitors, such as captopril, enalapril and lisinopril; and agents which decrease, block, inhibit, abrogate or interfere with TNFα production and/or synthesis, such as, but not limited to, MAP kinase inhibitors. Other TNFα antagonists are known in the art or can be readily identified by routine screening of candidates for their effect on TNFα activity.

Anti-TNFα Antibodies

As used herein, an anti-tumor necrosis factor alpha antibody decreases, blocks, inhibits, abrogates or interferes with TNFα activity *in vivo*. In a preferred embodiment, the antibody specifically binds the antigen. The antibody can be polyclonal or monoclonal, and the term antibody is intended to encompass both polyclonal and monoclonal antibodies. The terms polyclonal and monoclonal refer to the degree of homogeneity of an antibody preparation, and are not intended to be limited to particular methods of production. Single chain antibodies, and chimeric, humanized or primatized (CDR-grafted antibodies, with or without framework changes), or veneered antibodies, as well as chimeric, CDR-grafted or veneered single chain antibodies, comprising portions derived from different species, and the like are also encompassed by the present invention and the term "antibody".

In a particular embodiment, the anti-TNFα antibody is a chimeric antibody. In a preferred embodiment, the anti-TNFα antibody is chimeric monoclonal antibody cA2 (or an antigen binding fragment thereof) or murine monoclonal antibody A2 (or an antigen binding fragment thereof), or has an epitopic specificity similar to that of chimeric antibody cA2, murine monoclonal antibody A2, or antigen binding fragments thereof, including antibodies or antigen binding fragments reactive with the same or a functionally equivalent epitope on human TNFα as that bound by chimeric antibody cA2 or murine monoclonal antibody A2, or antigen binding fragments thereof. Antibodies with an epitopic specificity similar to that of chimeric antibody cA2 or murine monoclonal antibody A2 include antibodies which can compete with chimeric antibody cA2 or murine monoclonal antibody A2 (or antigen binding fragments thereof) for binding to human TNFα. Such antibodies or

fragments can be obtained as described above. Chimeric antibody cA2, murine monoclonal antibody A2 and methods of obtaining these antibodies are also described in Le *et al.*, U.S. Patent No. 5,656,272; Le *et al.*, U.S. Patent No. 5,698,195; U.S. Patent No. 5,919,452; U.S. Application No. 08/192,093 (filed February 4, 1994); Le, J. *et al.*, International Publication No. WO 92/16553 (published October 1, 1992); Knight, D.M. *et al.*, *Mol. Immunol.*, *30*:1443-1453 (1993); and Siegel, S.A. *et al.*, *Cytokine, 7*(1):15-25 (1995), which references are each entirely incorporated herein by reference. Chimeric antibody cA2 is also known as infliximab and REMICADE® antibody.

Chimeric antibody cA2 consists of the antigen binding variable region of the high-affinity neutralizing mouse anti-human TNFα IgG1 antibody, designated A2, and the constant regions of a human IgG1, kappa immunoglobulin. The human IgG1 Fc region improves allogeneic antibody effector function, increases the circulating serum half-life and decreases the immunogenicity of the antibody. The avidity and epitope specificity of the chimeric antibody cA2 is derived from the variable region of the murine antibody A2. In a particular embodiment, a preferred source for nucleic acids encoding the variable region of the murine antibody A2 is the A2 hybridoma cell line.

Chimeric A2 (cA2) neutralizes the cytotoxic effect of both natural and recombinant human TNFα in a dose dependent manner. From binding assays of chimeric antibody cA2 and recombinant human TNFα, the affinity constant of chimeric antibody cA2 was calculated to be $1.04 \times 10^{10} M^{-1}$. Preferred methods for determining monoclonal antibody specificity and affinity by competitive inhibition can be found in Harlow, *et al.*, *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1988; Colligan *et al.*, eds., *Current Protocols in Immunology,* Greene Publishing Assoc. and Wiley Interscience, New York, (1992, 1993); Kozbor *et al.*, *Immunol. Today, 4*:72-79 (1983); Ausubel *et al.*, eds. *Current Protocols in Molecular Biology,* Wiley Interscience, New York (1987, 1992, 1993); and Muller, *Meth. Enzymol.*, *92*:589-601 (1983), which references are entirely incorporated herein by reference.

In a particular embodiment, chimeric antibody cA2 is produced by a cell line designated c168A and murine monoclonal antibody A2 is produced by a cell line designated c134A.

Additional examples of anti-TNFα antibodies (or antigen-binding fragments thereof) are described in the art (see, e.g., Aggarwal *et al.*, U.S. Patent No. 5,795,967; Möller, A. *et al.*, U.S. Patent No. 5,231,024; Möller, A. *et al.*, *Cytokine, 2*(3):162-169 (1990); U.S. Application No. 07/943,852 (filed September 11, 1992); Rathjen *et al.*, International Publication No. WO 91/02078 (published February 21, 1991); Rubin *et al.*, EPO Patent Publication No. 0 218 868 (published April 22, 1987); Yone *et al.*, EPO Patent Publication No. 0 288 088 (October 26, 1988); Liang, *et al.*, *Biochem. Biophys. Res. Comm., 137*:847-854 (1986); Meager, *et al.*, *Hybridoma, 6*:305-311 (1987); Fendly *et al.*, *Hybridoma, 6*:359-369 (1987); Bringman, *et al.*, *Hybridoma, 6*:489-507 (1987); and Hirai, *et al.*, *J. Immunol. Meth., 96*:57-62 (1987), which references are entirely incorporated herein by reference).

Suitable antibodies are available, or can be raised against an appropriate immunogen, such as isolated and/or recombinant antigen or portion thereof (including synthetic molecules, such as synthetic peptides) or against a host cell which expresses recombinant antigen. In addition, cells expressing recombinant antigen, such as transfected cells, can be used as immunogens or in a screen for antibody which binds receptor (see e.g., Chuntharapai *et al.*, *J. Immunol., 152:* 1783-1789 (1994); and Chuntharapai *et al.*, U.S. Patent No. 5,440,021).

Preparation of immunizing antigen, and polyclonal and monoclonal antibody production can be performed using any suitable technique. A variety of methods have been described (see e.g., Kohler *et al.*, *Nature, 256:* 495-497 (1975) and *Eur. J. Immunol., 6:* 511-519 (1976); Milstein *et al.*, *Nature, 266: 550-552 (1977);* Koprowski *et al.*, U.S. Patent No. 4,172,124; Harlow, E. and D. Lane, 1988, *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory: Cold Spring Harbor, NY); and *Current Protocols In Molecular Biology*, Vol. 2 (Supplement 27, Summer '94), Ausubel *et al.*, eds. (John Wiley & Sons: New York, NY), Chapter 11, (1991)). Generally, a hybridoma can be produced by fusing a suitable immortal cell line (e.g., a myeloma cell line such as SP2/0) with antibody producing cells. The

antibody producing cell, preferably those of the spleen or lymph nodes, can be obtained from animals immunized with the antigen of interest. The fused cells (hybridomas) can be isolated using selective culture conditions, and cloned by limiting dilution. Cells which produce antibodies with the desired specificity can be selected by a suitable assay (e.g., ELISA).

Other suitable methods of producing or isolating antibodies of the requisite specificity, including human antibodies, can be used, including, for example, methods by which a recombinant antibody or portion thereof are selected from a library, such as, for example, by phage display technology (see, e.g., Winters *et al.*, *Annu. Rev. Immunol., 12*:433-455 (1994); Hoogenboom *et al.*, WO 93/06213; Hoogenboom *et al.*, U.S. Patent No. 5,565,332; WO 94/13804, published June 23, 1994; Krebber *et al.*, U.S. Patent No. 5,514,548; and Dower *et al.*, U.S. Patent No. 5,427,908), or which rely upon immunization of transgenic animals (e.g., mice) capable of producing a full repertoire of human antibodies (see e.g., Jakobovits *et al., Proc. Natl. Acad. Sci. USA, 90*: 2551-2555 (1993); Jakobovits *et al., Nature, 362*: 255-258 (1993); Kucherlapati *et al.*, European Patent No. EP 0 463 151 B1; Lonberg *et al.*, U.S. Patent No. 5,569,825; Lonberg *et al.*, U.S. Patent No. 5,545,806; and Surani *et al.*, U.S. Patent No. 5,545,807).

The various portions of single chain antibodies, chimeric, humanized or primatized (CDR-grafted antibodies, with or without framework changes), or veneered antibodies, as well as chimeric, CDR-grafted or veneered single chain antibodies, comprising portions derived from different species, can be joined together chemically by conventional techniques, or can be prepared as a contiguous protein using genetic engineering techniques. For example, nucleic acids encoding a chimeric or humanized chain can be expressed to produce a contiguous protein. See, e.g., Cabilly *et al.*, U.S. Patent No. 4,816,567; Cabilly *et al.*, European Patent No. 0,125,023 B1; Boss *et al.*, U.S. Patent No. 4,816,397; Boss *et al.*, European Patent No. 0,120,694 B1; Neuberger, M.S. *et al.*, WO 86/01533; Neuberger, M.S. *et al.*, European Patent No. 0,194,276 B1; Winter, U.S. Patent No. 5,225,539; Winter, European Patent No. 0,239,400 B1; Queen *et al.*, U.S. Patent No. 5,585,089; Queen *et al.*, European Patent No. 0,451,216 B1; Adair *et al.*, WO 91/09967, published 11

July 1991; Adair *et al.*, European Patent No. 0,460,167 B1; and Padlan, E.A. *et al.*, European Patent No. 0,519,596 A1. See also, Newman, R. *et al., BioTechnology, 10:* 1455-1460 (1992), regarding primatized antibody, and Huston *et al.*, U.S. Patent No. 5,091,513; Huston *et al.*, U.S. Patent No. 5,132,405; Ladner *et al.*, U.S. Patent No. 4,946,778 and Bird, R.E. *et al., Science, 242:* 423-426 (1988)) regarding single chain antibodies.

In addition, antigen binding fragments of antibodies, including fragments of chimeric, humanized, primatized, veneered or single chain antibodies and the like, can also be produced. For example, antigen binding fragments include, but are not limited to, fragments such as Fv, Fab, Fab' and $F(ab')_2$ fragments. Antigen binding fragments can be produced by enzymatic cleavage or by recombinant techniques, for example. For instance, papain or pepsin cleavage can generate Fab or $F(ab')_2$ fragments, respectively. Antibodies can also be produced in a variety of truncated forms using antibody genes in which one or more stop codons has been introduced upstream of the natural stop site. For example, a chimeric gene encoding a $F(ab')_2$ heavy chain portion can be designed to include DNA sequences encoding the CH_1 domain and hinge region of the heavy chain.

Anti-TNFα antibodies suitable for use in the present invention are characterized by high affinity binding to TNFα and low toxicity (including human anti-murine antibody (HAMA) and/or human anti-chimeric antibody (HACA) response). An antibody where the individual components, such as the variable region, constant region and framework, individually and/or collectively possess low immunogenicity is suitable for use in the present invention. Antibodies which can be used in the invention are characterized by their ability to treat patients for extended periods with good to excellent alleviation of symptoms and low toxicity. Low immunogenicity and/or high affinity, as well as other undefined properties, may contribute to the therapeutic results achieved. "Low immunogenicity" is defined herein as raising significant HACA or HAMA responses in less than about 75%, or preferably less than about 50% of the patients treated and/or raising low titers in the patient treated (less than about 300, preferably less than about 100 measured with a

double antigen enzyme immunoassay) (see, e.g., Elliott *et al.*, *Lancet 344*:1125-1127 (1994), incorporated herein by reference).

As used herein, the term "antigen binding region" refers to that portion of an antibody molecule which contains the amino acid residues that interact with an antigen and confer on the antibody its specificity and affinity for the antigen. The antigen binding region includes the "framework" amino acid residues necessary to maintain the proper conformation of the antigen-binding residues.

The term antigen refers to a molecule or a portion of a molecule capable of being bound by an antibody which is additionally capable of inducing an animal to produce antibody capable of selectively binding to an epitope of that antigen. An antigen can have one or more than one epitope.

The term epitope is meant to refer to that portion of the antigen capable of being recognized by and bound by an antibody at one or more of the antibody's antigen binding region. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and have specific three dimensional structural characteristics as well as specific charge characteristics. By "inhibiting and/or neutralizing epitope" is intended an epitope, which, when bound by an antibody, results in loss of biological activity of the molecule containing the epitope, *in vivo* or *in vitro*, more preferably *in vivo*, including binding of TNFα to a TNFα receptor.

TNFα Receptor Molecules

As used herein, TNFα receptor molecules bind specifically to TNFα, and include the 55 kDa (p55 TNF-R) and the 75 kDa (p75 TNF-R) TNFα cell surface receptors and truncated forms of these receptors, comprising the extracellular domains (ECD) of the receptors or functional portions thereof (see, e.g., Corcoran *et al.*, *Eur. J. Biochem.*, *223*:831-840 (1994)). TNFα receptors (TNF-Rs) have been described in the art (see, e.g., Smith *et al.*., U.S. Patent No. 5,395,760; Smith *et al.*, U.S. Patent No. RE36,755; Smith *et al.*, U.S. Patent No. 5,712,155; Smith *et al.*, 5,945,397; Feldmann *et al.*, U.S. Patent No. 5,633,145; Feldmann *et al.*, U.S. Patent No. 5,863,786; Jacobs *et al.*, U.S. Patent No. 5,605,690; and Stauber *et al.*, *J. Biol.*

Chem., *263*:19098-19104 (1988), which references are incorporated herein by reference in their entirety). Truncated forms of TNF-Rs, comprising the ECD, have been detected in urine and serum as 30 kDa and 40 kDa TNFα inhibitory binding proteins (Engelmann, H. *et al.*, *J. Biol. Chem.*, *265*:1531-1536 (1990)). TNFα receptor multimeric molecules and TNFα immunoreceptor fusion molecules, and derivatives and fragments or portions thereof, are additional examples of TNFα receptor molecules. Preferred embodiments of the invention utilize soluble TNFα receptor molecules.

As used herein, TNFα receptor multimeric molecules comprise all or a functional portion of the ECD of two or more TNF-Rs linked via one or more polypeptide linkers or other nonpeptide linkers, such as polyethylene glycol (PEG). The multimeric molecules can further comprise a signal peptide of a secreted protein to direct expression of the multimeric molecule.

As used herein, TNFα immunoreceptor fusion molecules comprise at least one portion of one or more immunoglobulin molecules and all or a functional portion of one or more TNF-Rs. These immunoreceptor fusion molecules can be assembled as monomers, or hetero- or homo-multimers. The immunoreceptor fusion molecules can also be monovalent or multivalent. Examples of such TNFα immunoreceptor fusion molecules include TNF-R/IgG fusion proteins and TNF-R/F_c fusion proteins (e.g., p75TNF-R:F_c fusion proteins). ENBREL® receptor (etanercept) (Immunex Corp., Seattle, WA) is an example of a recombinant TNFα immunoreceptor fusion molecule. TNFα immunoreceptor fusion molecules and methods for their production have been described in the art (see, e.g., Lesslauer *et al.*, *Eur. J. Immunol.*, *21*:2883-2886 (1991); Ashkenazi *et al.*, *Proc. Natl. Acad. Sci. USA*, *88*:10535-10539 (1991); Peppel *et al.*, *J. Exp. Med.*, *174*:1483-1489 (1991); Kolls *et al.*, *Proc. Natl. Acad. Sci. USA*, *91*:215-219 (1994); Butler *et al.*, *Cytokine*, *6*(6):616-623 (1994); Baker *et al.*, *Eur. J. Immunol.*, *24*:2040-2048 (1994); Beutler *et al.*, U.S. Patent No. 5,447,851; and Srinivasan *et al.*, U.S. Patent No. 5,716,805, which references are entirely incorporated herein by reference). Methods for producing immunoreceptor fusion molecules can also be found in Capon *et al.*, U.S. Patent No. 5,116,964; Capon *et al.*, U.S. Patent No. 5,225,538; and Capon *et al.*,

Nature, 337:525-531 (1989), which references are entirely incorporated herein by reference.

Derivatives, fragments, regions and functional portions of TNFα receptor molecules which functionally resemble TNF-Rs are also encompassed by the term "TNFα receptor molecule". A functional equivalent or derivative of a TNFα receptor molecule refers to the portion of the TNFα receptor molecule, or the portion of the TNFα receptor molecule sequence which encodes the TNFα receptor molecule, that is of sufficient size and sequences to functionally resemble a TNF-R. For example, a functional equivalent of TNFα receptor molecule can contain a "SILENT" codon or one or more amino acid substitutions, deletions or additions (e.g., substitution of one acidic amino acid for another acidic amino acid; or substitution of one codon encoding the same or different hydrophobic amino acid for another codon encoding a hydrophobic amino acid). See Ausubel *et al.*, *Current Protocols in Molecular Biology*, Greene Publishing Assoc. and Wiley-Interscience, New York (1989).

TNFα receptor molecules suitable for use in the present invention are characterized by high affinity binding to TNFα (see, e.g., Feldmann *et al.*, International Publication No. WO 92/07076 (published April 30, 1992); Schall *et al.*, *Cell, 61*:361-370 (1990); and Loetscher *et al.*, *Cell, 61*:351-359 (1990), which references are entirely incorporated herein by reference) and possess low immunogenicity. TNFα receptor molecules which can be used in the invention are characterized by their ability to treat patients for extended periods with good to excellent alleviation of symptoms and low toxicity. Low immunogenicity and/or high affinity, as well as other undefined properties, may contribute to the therapeutic results achieved.

Administration

TNFα antagonists can be administered to a patient in a variety of ways. The routes of administration include intravenous including infusion and/or bolus injection, intradermal, transdermal (e.g., in slow release polymers), intramuscular, intraperitoneal, subcutaneous, topical, epidural, intranasal, oral, buccal, etc. routes.

Other suitable routes of administration can also be used, for example, to achieve absorption through epithelial or mucocutaneous linings. TNFα antagonists can also be administered by gene therapy, wherein a DNA molecule encoding a particular therapeutic protein or peptide is administered to the patient, e.g., via a vector, which causes the particular protein or peptide to be expressed and secreted at therapeutic levels *in vivo*. In addition, TNFα antagonists can be administered together with other components of biologically active agents, such as pharmaceutically acceptable surfactants (e.g., glycerides), excipients (e.g., lactose), stabilizers, preservatives, humectants, emollients, antioxidants, carriers, diluents and vehicles. If desired, certain sweetening, flavoring and/or coloring agents can also be added.

TNFα antagonists can be administered prophylactically or therapeutically to an individual prior to, simultaneously (concurrently) with or sequentially with other therapeutic regimens or agents (e.g., multiple drug regimens, adjuvant therapy), including with other therapeutic regimens or medications that are use in treating psoriasis, psoriatic skin lesions and/or psoriatic arthritis. Medications (i.e., drugs) suitable for combination therapies in accordance with the present invention include pain medications (analgesics), including but not limited to acetaminophen, codeine, propoxyphene napsylate, oxycodone hydrochloride, hydrocodone bitartrate and tramadol; methotrexate; Leflunomide; sulfasalazine; cyclosporine; gold salts; azathioprine; antimalarials; oral steroids (e.g., prednisone); colchicine; non-steroidal anti-inflammatories, including but not limited to salicyclic acid (aspirin), ibuprofen, indomethacin, celecoxib, rofecoxib, ketorolac, nambumetone, piroxicam, naproxen, oxaprozin, sulindac, ketoprofen, diclofenac, other COX-1 and COX-2 inhibitors, salicyclic acid derivatives, propionic acid derivatives, acetic acid derivatives, fumaric acid derivatives, carboxylic acid derivatives, butyric acid derivatives, oxicams, pyrazoles and pyrazolones, including newly developed anti-inflammatories. Other agents suitable for use in combination with TNFα antagonists include topical steroids, systemic steroids, glucocorticoids, antagonists of inflammatory cytokines, antibodies against T cell surface proteins, anthralin, coal tar, vitamin D analogs (including vitamin D3 and its analog (including 1,25-dihydroxy vitamin D3 and calcipotriene)), topical retinoids, oral retinoids

(including but not limited to etretinate, acitretin and isotretinoin), topical salicylic acid, hydroxyurea, minocycline, misoprostol, oral collagen, penicillamine, 6-mercaptopurine, nitrogen mustard, gabapentin, bromocriptine, somatostatin, peptide T, anti-CD4 monoclonal antibody, fumaric acid, polyunsaturated ethyl ester lipids, zinc, topical oils (including fish oils, nut oils and vegetable oils), aloe vera, topical jojoba, topical Dead Sea salts, topical capsaicin, topical milk thistle, topical witch hazel, moisturizers and topical Epson salts. Therapeutic regimens suitable for use in combination with TNFα antagonists for treating psoriasis, psoriatic lesions or psoriatic arthritis include but are not limited to plasmapheresis, phototherapy with ultraviolet light B, psoralen combined with ultraviolet light A (PUVA), photochemotherapy and sunbathing.

TNFα antagonists that are administered simultaneously with other therapeutic agents can be administered in the same or different compositions. Multiple TNFα antagonists (i.e., two or more different TNFα antagonists) can also be administered.

TNFα antagonists can be formulated as a solution, suspension, emulsion or lyophilized powder in association with a pharmaceutically acceptable parenteral vehicle. Examples of such vehicles are water, saline, Ringer's solution, dextrose solution, and 5% human serum albumin. Liposomes and nonaqueous vehicles such as fixed oils can also be used. The vehicle or lyophilized powder can contain additives that maintain isotonicity (e.g., sodium chloride, mannitol) and chemical stability (e.g., buffers and preservatives). The formulation can be sterilized by commonly used techniques. Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences.

A "therapeutically effective amount" of TNFα antagonist is defined herein as that amount, or dose, of TNFα antagonist that, when administered to an individual, is sufficient for therapeutic efficacy (e.g., an amount sufficient for significantly reducing, eliminating or inducing an improvement in symptoms or signs, or both symptoms or signs, associated with psoriasis, psoriatic lesions or psoriatic arthritis). A therapeutically effective amount is also that amount, or dose, of TNFα antagonist that, when administered to an individual, is sufficient to induce an improvement in

the individual's condition as measured according to any indicator that reflects the severity of the individual's psoriatic lesions. One or more such indicators can be assessed for determining whether the amount of TNFα antagonist is sufficient. In one embodiment, the TNFα antagonist is administered in an amount sufficient to induce an improvement over baseline in either the psoriasis area and severity index (PASI) (Fredriksson and Pettersson, *Dermatologica*, 157:238-244 (1978)) or the Target Lesion Assessment Score. In another embodiment, both indicators are used. The PASI rates the scaling, erythema and thickness of psoriasis plaques and the body surface area covered by psoriasis. It ranges from 0 to 72, with higher scores indicating severe disease. Using the Psoriasis Target Lesion Assessment Score to measure sufficiency of treatment involves determining for an individual psoriatic lesion whether improvement has occurred in one or more of the following, each of which is separately scored: plaque elevation, amount and degree of scaling or degree of erythema and target lesion response to treatment. Psoriasis Target Lesion Assessment Score is determined by adding together the separate scores for all four of the aforementioned indicia and determining the extent of improvement by comparing the baseline score and the score after treatment has been administered.

The dosage administered to an individual will vary depending upon a variety of factors, including the pharmacodynamic characteristics of the particular TNFα antagonist, and its mode and route of administration; size, age, sex, health, body weight and diet of the recipient; nature and extent of symptoms of the disease or disorder being treated, kind of concurrent treatment, frequency of treatment, and the effect desired. A therapeutically effective amount of a TNFα antagonist that is administered simultaneously with other therapeutic agents can be an amount which is the same as or different from the dosage of the TNFα antagonist when administered alone depending upon the kind of concurrent treatment.

The therapeutically effective amount can be administered in single or divided doses (e.g., a series of doses separated by intervals of days, weeks or months) or in a sustained release form, depending upon factors such as nature and extent of symptoms, kind of concurrent treatment and the effect desired. Other therapeutic regimens or agents can be used in conjunction the present invention. Adjustment

and manipulation of established dosage ranges are well within the ability of those skilled in the art.

Once a therapeutically effective amount has been administered, a maintenance amount of TNFα antagonist can be administered to the individual. A maintenance amount is the amount of TNFα antagonist necessary to maintain the reduction or elimination of symptoms or signs, or both symptoms and signs, achieved by the therapeutically effective dose. The maintenance amount can be administered in the form of a single dose or a series of doses separated by intervals of days or weeks (divided doses).

Second or subsequent administrations can be administered at a dosage which is the same, less than or greater than the initial or previous dose administered to the individual. Thus, multiple doses of a therapeutically effective amount of TNFα antagonist (separated by intervals of days, weeks or months) can be administered to the individual. A second or subsequent administration is preferably during or immediately prior to recurrence, relapse or a flare-up of the disease or symptoms of the disease. For example, the second and subsequent administrations can be given between about one day to 30 weeks or more from the previous administration. Two, three, four or more total administrations can be delivered to the individual, as needed. The terms "recurrence", "flare-up" and "relapse" are defined to encompass the reappearance of one or more symptoms of the disease state.

In a preferred embodiment, TNFα antagonists are formulated into unit dosage forms for administration to a patient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and animals, each unit containing a predetermined quantity of active material calculated to produce the desired pharmaceutical effect in association with the required pharmaceutical diluent, carrier or vehicle. The specifications for the unit dosage forms are dictated by and dependent on the unique characteristics of the active ingredient (i.e., the particular TNFα antagonist), the particular effect to be achieved, the route of administration, and the desired duration of treatment. Thus, the dosage levels of active ingredient in a unit dosage form can be varied so as to obtain an amount of active ingredient effective to achieve activity in accordance with the

desired method of administration. If desired, the unit dosage can be such that the daily requirement for active compound is in one dose or divided among multiple doses for administration (e.g., two to four or more times per day).

Dosage forms (composition) suitable for internal administration generally contain from about 0.1 milligram to about 500 milligrams of active ingredient per unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

The present invention will now be illustrated by the following Example, which is not intended to be limiting in any way.

EXAMPLE

A 48-year old female patient with a history of fairly severe psoriasis and Crohn's disease was treated with a single infusion (5 mg/kg) of the anti-TNFα antibody cA2 (week 0) and four subsequent infusions of placebo (one each at week 12, 20, 29 and 37). The patient also had a history of arthritis and arthralgias.

The anti-TNFα antibody cA2 was supplied as a sterile solution containing 5 mg cA2 per ml of 0.01 M phosphate-buffered saline in 0.15 M sodium chloride with 0.01% polysorbate 80, pH 7.2. The placebo vials contained 0.1% human serum albumin in the same buffer. Before use, the appropriate amount of cA2 or placebo was diluted to 300 ml in sterile saline, and administered intravenously via a 0.2 μm in-line filter over 2 hours.

Approximately 2 weeks following infusion with cA2, the patient exhibited dramatic improvement in her psoriasis, as well as improvement in her Crohn's disease. Approximately 8 to 12 weeks following treatment with cA2, both her psoriasis and Crohn's disease symptoms returned. Neither disease improved after the patient was crossed over to placebo at week 12.

Approximately 10 weeks following infusion with cA2, the patient complained of neck and shoulder myalgias and arthralgias which were treated with ibuprofen. The intensity of the symptoms was rated as "severe". The symptoms

were musculoskeletal in origin, not associated with a neurological defect and improved with massage. The symptoms continued but the intensity decreased 13 weeks later. The patient was antinuclear antibodies (ANA) positive, with titers of 1:80 at baseline, 1:640 at 12 weeks and 1:160 at 48 weeks. Antibodies to double-stranded DNA were normal (< 70 IU/ml) at baseline and at 48 weeks but were elevated (145 IU/ml) at 12 weeks. These events were considered not serious and probably not related to anti-TNFα antibody treatment.

Over the next almost 3 years, the patient was treated with methotrexate and other standard medications. Approximately 37 months following the initial treatment with cA2, the patient was again treated with an infusion of 5 mg/kg of the anti-TNFα antibody cA2. The patient again exhibited considerable improvement in both her psoriasis and Crohn's disease following this second treatment with anti-TNFα antibody.

Although approximately one week following the second infusion of cA2, the patient developed urticaria, arthralgias and myalgias, this condition was treated with methylprednisolone with improvement. The patient had not experienced this adverse event following her first infusion of cA2.

The teachings of all the articles, patents and patent applications cited herein are incorporated by reference in their entirety.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. Use of an anti-TNFα antibody or an antigen-binding fragment thereof for the manufacture of a medicament for use in the treatment of psoriasis or psoriatic lesions in an individual in need thereof.

2. Use according to Claim 1 wherein the antibody or fragment is a chimeric antibody or chimeric fragment, wherein said chimeric antibody or chimeric fragment comprises a non-human variable region specific for TNFα or an antigen-binding portion thereof and a human constant region.

3. Use according to Claim 2 wherein the chimeric antibody or chimeric fragment competitively inhibits binding of monoclonal antibody cA2 to human TNFα.

4. Use according to Claim 3 wherein the chimeric antibody is the cA2 antibody.

5. A method of treating psoriasis or psoriatic lesions in an individual in need thereof comprising administering a therapeutically effective amount of an anti-TNFα antibody or antigen-binding fragment thereof to the individual.

6. The method of Claim 5 wherein the antibody or fragment is a chimeric antibody or chimeric fragment, wherein said chimeric antibody or chimeric fragment comprises a non-human variable region specific for TNFα or an antigen-binding portion thereof and a human constant region.

7. The method of Claim 6 wherein the chimeric antibody or chimeric fragment competitively inhibits binding of monoclonal antibody cA2 to human TNFα.

8. A method of Claim 6 wherein the chimeric antibody is monoclonal antibody cA2.